Supplemental Expert Report
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I have had the opportunity to review supplemental reports submitted by experts for W. R. Grace & Co., and here set forth my rebuttal opinions to points raised in those reports.

(1) Dr. Anderson holds the opinion that it is scientifically acceptable to estimate an individual's exposure solely to Grace products, and determine whether that exposure alone would double the risk of mesothelioma or lung cancer. If the risk estimate for exposure to Grace products alone does not double the risk, is her opinion that these exposures are not a substantial contributing cause to the development of any individual lung cancer or mesothelioma. She relies upon exposure estimates from Dr. Lees and estimates of relative risk from Dr. Moolgavkar to develop her model, and concludes that the exposures to Grace products alone are quite low, while the amount of exposure required to double the risk of mesothelioma or lung cancer is quite high. Here I will address (1) Dr. Anderson's and Moolgavkar's estimates of the risk of disease from exposure to asbestos (2) what occupations have had a substantial exposure to asbestos, and so are at risk of disease from that exposure (3) how one cannot subtract all other exposures and act as if the exposure to a Grace product was the only exposure, and (4) the way in which each asbestos exposure is a substantial contributing cause to an asbestos-related disease.

Risk estimates:

On page 3 Dr. Anderson cites the permissible exposure limit (PEL) set by the Occupational Safety and Health Administration for exposure to asbestos as a benchmark, stating the PEL is a level of exposure that is considered by a federal agency to be acceptable under occupational conditions today. It is important to point out that this limit of 0.1 f/ml, or a lifetime exposure of 4.5 f/ml-yrs, is considered by OSHA to carry a significant risk of mesothelioma and lung cancer. In the 1994 preamble to the asbestos rule, OSHA states: "...OSHA's risk assessment also showed that reducing exposure to 0.1 f/ cc would further reduce, but not eliminate, significant risk. The excess cancer risk at that level would be reduced to a lifetime risk of 3.4 per 1,000 workers and a 20 year exposure risk of 2.3 per 1,000 workers." [1] OSHA makes it clear in the preamble to the asbestos standard of 0.1 f/ml that this PEL was chosen because measurement of exposures lower than 0.1 f/ml was not technically feasible or reliable.

Dr. Moolgavkar is of the opinion that we have little direct epidemiologic evidence of disease from asbestos at levels of exposure to asbestos below 15f/ml-yr, and therefore cannot determine whether or not a threshold exists below which asbestos exposure carries no risk of disease. He states "we simply do not know whether or not a threshold exists". He relies upon a paper by Hodgson and Darnton [2] to support the statement. In this paper the authors assign a risk of mesothelioma and lung cancer to different levels of asbestos exposure. They

[1] Occupational Exposure to Asbestos - 59:40964-41162 published 08/1994
[2] Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg. 2000 Dec;44(8):565-601.

extrapolate from evidence of disease at higher levels to estimate risk at lower levels, the exact approach criticized by Dr. Moolgavkar. In Table 11 the authors estimate a risk of mesothelioma at cumulative exposures of 0.005 f/ml-yr and lower, and from this it is clear these authors do not postulate a threshold below which asbestos carries no risk of disease, and they state "Taking this evidence together we do not believe there is a good case for assuming any threshold for mesothelioma risk." Hodgson and Darnton's opinion is in keeping with that of national and international public health and regulatory agencies, including OSHA, the Environmental Protection Agency, the US National Toxicology Program, and the World Health Organization. [3]

Dr. Anderson quotes Dr. Moolgavkar as saying that the risk of mesothelioma doubles after exposure to chrysotile asbestos at cumulative exposures of 8.9 f/ml-yrs (p. 5 of her report). Hodgson and Darnton [4], in the article relied upon by Dr. Moolgavkar, estimate that exposure to chrysotile asbestos at a cumulative dose of 1 f/ml-yr gives a maximum increase of 20 deaths from mesothelioma over the lifetime of 100,000 exposed, and with a best estimate of 5/100,000 exposed. The "background" rate of mesothelioma is generally accepted as 1/1,000,000 per person annually [5]; an exposure of 1 f/ml-yr more than doubles the risk for mesothelioma, while Dr. Anderson states a doubling does not occur until exposure reaches 9 f/ml-yrs. Other research estimate higher risks at a cumulative exposure of 1 f/ml-yr; Iwatsubo reported a 4 fold increase in risk of mesothelioma from exposures below 1 f/ml-years,[6] and OSHA states at an exposure level of 1f/ml as a TWA leads to a lifetime excess cancer risk of 3.4 per 1,000 workers and with a 20 year exposure an excess cancer risk of 2.3 per 1,000 workers.[7] (Please note, as described in more detail below, that a doubling of risk is not needed to attribute a mesothelioma to asbestos exposure; any exposure must be assessed as to whether

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[3] World Health Organization (1998). Environmental Health Criteria 203: Chrysotile Asbestos; World Health Organization (2006); Elimination of Asbestos-Related Diseases. Geneva, Switzerland; National Toxicology Program; Report on Carcinogens, Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service 2005; Occupational Exposure to Asbestos - 59:40964-41162 published 08/1994

[4] Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg. 2000 Dec;44(8):565-601.

[5] Discussion: Part 8 Annals of the New York Academy of Sciences 643 (1), 223–227

[6] Iwatsubo Y, Pairon JC, Boutin C, Menard O, Massin N, Caillaud D, Orlowski E, Galateau-Salle F, Bignon J, Brochard P. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. Am J Epidemiol. 1998 Jul 15;148(2):133-42.; Magnani C, Agudo A, Gonzalez CA, Andrion A, Calleja A, Chellini E, Dalmasso P,Escolar A, Hernandez S, Ivaldi C, Mirabelli D, Ramirez J, Turuguet D, Usel M, Terracini B. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. Br J Cancer. 2000 Jul;83(1):104-11; Lin RT, Takahashi K, Karjalainen A, Hoshuyama T, Wilson D, Kameda T, Chan CC, Wen CP, Furuya S, Higashi T, Chien LC, Ohtaki M. Ecological association between asbestos-related diseases and historical asbestos consumption: an international analysis. Lancet. 2007 Mar 10;369(9564):844-9.

[7] Occupational Exposure to Asbestos - 59:40964-41162 published 08/1994 Occupational Safety and Health Administration

that exposure is a substantial contributing cause. I include these numbers here to show that the level of asbestos exposure needed to double the risk of mesothelioma is substantially lower than the numbers presented by Dr. Anderson.)

The analysis presented by Hodgson and Darnton is a conservative estimate of the risk of chrysotile asbestos as the sole exposure. Asbestos exposed individuals are almost always exposed to a mix of fiber types, and the calculation of the risk from one fiber type alone is usually not relevant to the risk in a population of exposed individuals. The risk estimated by Hodgson and Darnton for other types of asbestos are substantially higher, with an increased risk estimated at cumulative exposure levels as low as 0.005 f/ml-yrs.

Which occupations have a substantial risk of asbestos-related disease?

Dr. Anderson creates five categories of exposure. Groups A, B and C personally handled asbestos-containing products, through mixing, removing, cutting or installing the product; Groups D and E were at a site or in a space where asbestos-containing products were being installed, removed, or cut by others. She describes groups D and E this way: "Although it is possible for any of these people to experience some exposure during a time when installation, mixing, removal, or cutting of asbestos containing products by others was taking place, it can be inferred that exposure to these people is limited in its frequency."

Group D or E includes sheet metal workers, carpenters, and laborers – construction workers who do not use asbestos products as part of their craft, but work in the vicinity of other crafts who do. These occupations have had a significant impact from asbestos-related disease. A proportional analysis of cause of death (PMR) among 331 New York sheet metal workers found six deaths attributable to mesothelioma; 2% of all deaths in this cohort due to mesothelioma, which is 20,000 times the background rate of 1 case per 1 million people.[8] In addition to the risk of mesothelioma, sheet metal workers have a significant amount of non-malignant disease from asbestos; over 35% of sheet metal workers with more than 20 years in the trade had pleural plaques or asbestosis. [9]

A study of 27,362 deaths among carpenters found 121 mesotheliomas, 0.4%, again orders of magnitude higher than the expected background rate of 1 case per 1 million people. Among other construction workers that have no direct contact with asbestos insulation, there were 20 mesothelioma deaths were found among 11,685 deaths among laborers (0.17%), and a significant excess was also found among electricians (PMR 356).[10] The number of

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[8] Michaels D, Zoloth S. Asbestos disease in sheet metal workers: proportional mortality update. Am J Ind Med. 1988;13(6):731-4.

[9] Welch LS, Michaels D, and Zoloth S. Asbestos-Related Disease among Sheet Metal Workers. American Journal of Industrial Medicine 25:635-48, 1994

[10] Robinson CF, Petersen M, Palu S. Mortality patterns among electrical workers employed in the U.S. construction industry, 1982-1987. Am J Ind Med. 1999 Dec;36(6):630-7; Robinson CF, Petersen M, Sieber WK, Palu S, Halperin WE.
Mortality of Carpenters' Union members employed in the U.S. construction or wood products industries, 1987-1990. Am J Ind Med. 1996 Dec;30(6):674-94.

mesothelioma deaths found on death certificates is likely to be an under-estimate, and the actual rate of mesothelioma in these construction workers is likely to be higher, since there was not a specific code for mesothelioma until the 1999 edition of the International Classification of Diseases (ICD-10). To illustrate this point, one study reported that only 12% of mesotheliomas in the Mass Cancer Registry between 1982 and 1987 were later identified in a review of death certificates using underlying cause of death codes for pleural and peritoneal tumors (coded with the ICD-9).[11] Yet even if these numbers are under-estimates, they exceed Dr. Anderson's risk estimate by orders of magnitude.

Mesothelioma incidence in the US is still increasing, despite estimates to the contrary. From 1999 to 2004, the number of deaths from mesothelioma each year increased from 2,484 to 2,657. [12]

One cannot subtract all other exposures and act as if the exposure to a Grace product was the only exposure

As noted above, Dr. Anderson's analysis is based on the presumption that it is scientifically acceptable to estimate the exposure solely to Grace products, and determine whether that exposure would double the risk of mesothelioma or lung cancer. If the risk estimates for exposure to only Grace products do not double the risk, is her opinion that these exposures are not a substantial contributing cause to the development of any individual's lung cancer or mesothelioma. Dr. Moolgavkar holds a similar opinion when he states on page 7 of his report that "the only way to determine whether a specific exposure to asbestos was a factor in causing a claimant's disease is to conduct an explicit evaluation of the role of that asbestos exposure in causing the disease relative to the risk of developing the disease spontaneously and the additional risks imposed by other exposures, including other asbestos exposures."

Examining the question of causation of disease in an individual, generally involves four questions: (1) was the individual exposed to a toxic agent (2) does the agent cause the disease present in the individual; (3) was the individual exposed to this substance at a level where disease has occurred in other settings; and (4) have other competing explanations for the disease been excluded? [13] There is no reasonable dispute regarding Question 2, that asbestos causes mesothelioma. Additionally, there are no well-accepted competing explanations regarding mesothelioma which must be excluded, resolving Question 4. As a result, when considering the issue of causation of a mesothelioma, once an occupational or para-occupational exposure to asbestos has been established (Question 1), the sole question (Question 3) remaining for examination is whether the exposure or set of exposures of that individual is similar to exposures that have been documented to cause mesothelioma in others.

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[11] Davis LK, Martin TR, Kligler B. Use of death certificates for mesothelioma surveillance. Public Health Rep. 1992 Jul-Aug;107(4):481-3.

[12] National Occupational Respiratory Mortality System, CDC/NIOSH: http://webappa.cdc.gov/ords/norms.html

[13] Rempel DM, Harrison RJ, Barnhart S. Work-related cumulative trauma disorders of the upper extremity.JAMA. 1992 Feb 12;267(6):838-42; Rosenstock L, Cullen M, Redlich C, Brodkin D. Textbook of Clinical Occupational and Environmental Medicine. Elsevier Saunders 2005

Answering Question 3 in the affirmative does not require a doubling of risk in an epidemiological study, but rather an assessment of all the information available. (For additional discussion see my publication *Asbestos Exposure Causes Mesothelioma, But Not This Asbestos Exposure: An Amicus Brief to the Michigan Supreme Court,* which is attached as an appendix.)

The same approach applies to a determination whether a lung cancer is caused by asbestos exposure. Since there are other well accepted competing explanations for a cause of lung cancer (Question 4) the information needed is necessarily somewhat different than in the case of mesothelioma, but the same approach holds when examining the question of causation of disease in an individual.

Once we have established that an individual's disease was caused by asbestos, using the logic model above, we can then address the question of whether a particular exposure was a substantial contributing cause to the development of that disease.

When Dr. Moolgavkar states on page 7 of his report that "the only way to determine whether a specific exposure to asbestos was a factor in causing a claimant's disease is to conduct an explicit evaluation of the role of that asbestos exposure in causing the disease relative to the risk of developing the disease spontaneously and the additional risks imposed by other exposures, including other asbestos exposures," he makes this statement in response to my expressed opinion that each and every exposure to asbestos is a factor in causing asbestos-related disease. He gives the example of an individual who smoked two packs of cigarettes a day for 40 years and develops lung cancer, and who claims that secondhand smoke was an important factor in his disease. The example given by Dr. Moolgavkar is chosen as to make my opinion seem absurd.

But consider this example instead. A man smoked one pack of cigarettes per day for 20 years, and develops lung cancer. Did the single cigarette he smoked on July 15, 1962 at 10 am substantially contribute to his lung cancer? Dr. Moolgavkar would say no, so we must subtract that cigarette from his total dose. Apply the same analysis to the cigarette that he smoked on July 15, 1962 at 1 pm, and then to each individual cigarette that he smoked. Looking at the impact of one cigarette at a time, Dr. Moolgavkar would subtract the effect of each individual cigarette. The end result is to conclude that cigarette smoking did not cause this man's lung cancer, which is clearly an absurd conclusion.

Then consider this example. The same man smoked cigarettes manufactured by 20 different companies over the 20 years in which he smoked. If his smoking was equally distributed among each of these 20 companies, then each company contributed 5% of his total dose. Could this man have developed lung cancer if you removed the cigarettes manufactured by one of these companies from his total dose? Everyone would agree this would be the case, and so Dr. Moolgavkar would say that this company's product was not a substantial contributing factor to the development of this man's lung cancer. Of course the same analysis would apply if you looked at the impact of each of these 20 companies in comparison to the other 19 companies combined; again you would have to conclude that his lung cancer was not caused by smoking cigarettes, and again this is clearly an absurd conclusion.

More details on my opinion that *each exposure to asbestos is a substantial contributing cause to an asbestos related disease* is presented in my initial expert report.

(2) Dr. Moolgavkar states that there is accumulating epidemiological evidence that high-dose chest radiation for the treatment of cancer causes mesothelioma, and cites studies by Tward (2006), Teta (2007) and Travis (2005). These three papers have some significant methodological limitations, and do not support the conclusion that chest radiation causes mesothelioma:

> The paper by Travis focuses on second cancers among testicular cancer patients, using 14 population-based tumor registries in Europe and North America. The authors report an increased number of malignant mesothelioma among testicular cancer survivors. However they have no information on which individuals received radiation therapy to the chest, and estimate that only about 16% of testicular cancer patients in this series who received radiation may have received radiation to the chest. Therefore, even though there is an excess risk of mesothelioma among testicular cancer survivors is not possible in this study to attribute that to radiation exposure, since we do not know which patients received chest radiation.
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> The paper by Tward reports on the risk of second cancers among individuals treated for non-Hodgkin's lymphoma, using data from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute. The patients who received any radiation were more likely to develop a mesothelioma; however as with the prior paper, there was no information on which patients received chest radiation.
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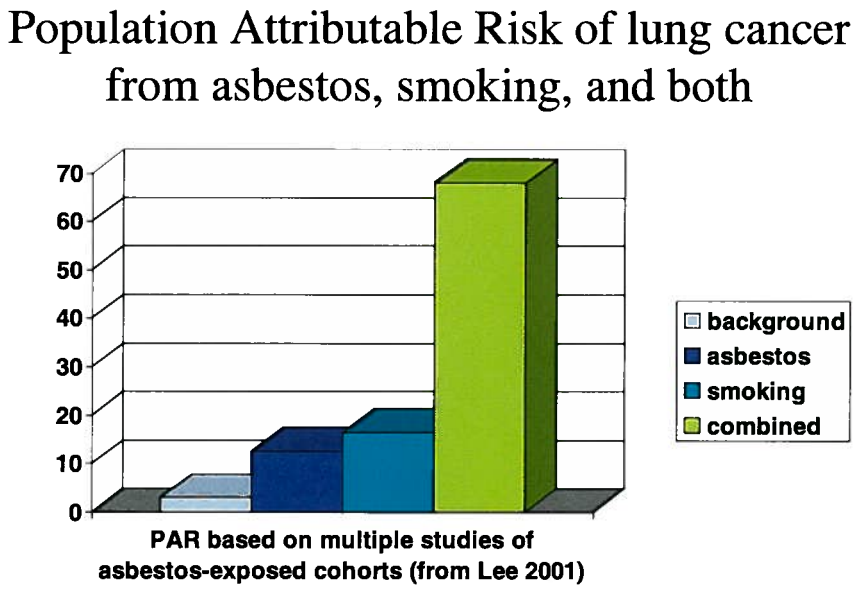
> The third paper by Teta looks at the risk of mesothelioma among individuals after therapeutic radiation for lymphoma. As with the prior papers there was no information available on which lymphoma patients received chest radiation. Dr. Teta does state in this publication, on page 1435, that the report from Travis (described above) found a statistically significant increase of plural mesothelioma among men who received super diaphragmatic radiation. This is incorrect; the paper by Travis did not have information on the location of radiation treatment.

Therefore even though this literature suggests that there may an increased risk of mesothelioma among cancer survivors, one cannot attribute this increased risk to chest irradiation. The cancer survivors in these studies had an increased risk in a range of cancers, including lung cancer, brain cancer, renal cancer, bladder cancer, melanoma and hematological malignancies. Travis (2005) states in the discussion: "Although the discussion above focuses on treatment as the primary explanation for the observed excesses, it should be kept in mind that elevated patterns of solid tumor risk may also reflect the influence of natural history, diagnostic surveillance, and shared etiologic factors."

These three studies included no information on asbestos exposure among the cancer survivors; such information is not included in the SEER data. Since asbestos is known to be the cause of 80-90% of mesotheliomas, a study of the causes of mesothelioma without information on asbestos would be like a study to see if individuals who took herbal supplements were more likely to get lung cancer without knowing smoking history. If smokers were more likely to take herbal supplements, a risk thought to come from the supplements was really due to smoking.

(3) Dr. Moolgavkar states on page 9 that a multiplicative relative risk for joint exposure to tobacco and asbestos "simply means that the relative risk for lung cancer associated with asbestos exposure is the same in non-smokers and smokers". Let's agree this is true, and calculate the population attributable risk (PAR) from asbestos exposure among smokers. The population attributable risk is the proportion of all lung cancers in the general population that is caused by the risk factor under consideration. You can see from the figure below that exposing a smoker to asbestos greatly increases his likelihood of lung cancer; 68% of lung cancers among smoking asbestos-exposed people are attributable to the combined exposure of asbestos and smoking, with 3% due to background, 12.6% to asbestos alone, and 16.5% to smoking alone (for a total of 100% of lung cancers attributable to one of the four factors). The pattern seen in the graph below results from the multiplicative risk of asbestos and smoking.



(4) Dr. Moolgavkar states on page 12 that the results of the updated analysis of the Libby cohort by Sullivan (2007) are consistent with the findings reported by McDonald; Dr. Moolgavkar concludes that both studies support the estimate that a cumulative amosite asbestos exposure of 100f/ml-yr leads to a relative risk of 1.36 for lung cancer. Sullivan's risk estimates are in fact much lower. Sullivan reports an SMR of 1.8 in the group with an exposure estimate of 24-99 f/yr, and the group with 4-25 f/yr had an SMR of 1.6. The confidence intervals for these two SMRs both include an SMR of 2, meaning the data is compatible with a doubling of risk at a level of exposure as low as 4 f/yr.

(5) Dr. Moolgavkar states on page 7 that the fraction of mesothelioma is occurring in individuals with no history of exposure to asbestos ranges from 22/80 percent in epidemiologic studies. He does not specifically cite the papers from which these numbers are derived, but a recent paper by Leigh [14] found that if exposure to asbestos was determined through both interview and pathologic examination of the lung, 90% of mesotheliomas in Australia had evidence of prior asbestos exposure. Further discussion of the proportion of mesotheliomas caused by asbestos can be found in my publication *Asbestos Exposure Causes Mesothelioma, But Not This Asbestos Exposure: An Amicus Brief to the Michigan Supreme Court,* which is attached as an appendix.

(6) Dr. Moolgavkar concludes, in his analysis of the study by McDonald (1988) that the health consequences of exposure to a small amount of tremolite are minimal. The study he references included 194 workers, with 4 lung cancers detected when 3 were expected; this population is much too small a sample to estimate risk of lung cancer. In addition, in contrast to Dr. Moolgavkar's opinion that a small amount of tremolite carries no risk, there is a great deal of literature that concludes there a significant risk of disease after exposure to a small amount of tremolite (amphibole); Hodgson and Darnton estimate as high as 80 deaths from mesothelioma per 100,000 exposed to 0.1 f/ml-yrs cumulative exposure .

(7) Dr. Anderson states that there are numerous case-control cohort and proportional mortality ratio studies that have been conducted on auto mechanics and auto workers that have been exposed to chrysotile asbestos, and that these studies do not support a causal association between brake work and mesothelioma. My opinions on the question of whether exposure to asbestos during work on asbestos containing brakes can cause mesothelioma is described in more detail in the paper in the appendix.

(8) Dr. Weill expressed the opinion that there is no consensus on the use of HRCT for the diagnosis of asbestosis. In support of my opinion that HRCT is widely accepted, I refer the reader to the 2004 American Thoracic Society document, *The Diagnosis and Initial Management of Non-Malignant Disease Related to Asbestos.* The document states that HRCT has an important role in the diagnosis of asbestosis when expert readers disagree about interpretation of a high-quality chest film, if the chest film is of poor quality, and when pulmonary function is abnormal but the chest x-ray is normal. As described in my previous report this document represents the consensus of the American Thoracic Society, the leading professional organization of pulmonary disease specialists; more recent literature also supports the important role of HRCT in the diagnosis of asbestosis. [15]

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[14] Leigh et. al., Malignant Mesothelioma in Australia, 1945-2000. Am J Ind Med 2002; 41:188-201

[15] Suganuma N, Kusaka Y, Hering KG, Vehmas T, Kraus T, Parker JE, Shida H; International CT Classification Study Group.. Selection of reference films based on reliability assessment of a classification of high-resolution computed tomography for pneumoconioses. Int Arch Occup Environ Health. 2006 Jun;79(6):472-6; Meirelles GS, Kavakama JI, Jasinowodolinski D, Nery LE, Terra-Filho M, Rodrigues RT, Neder JA, Napolis LM, Bagatin E, D'Ippolito G, Müller NL Pleural

(9) Dr. Weill expressed the opinion that the DLCO is not the most sensitive test for the diagnosis of asbestosis. In support of my opinion that DLCO is often reported to be the most sensitive test, I again refer the reader to the ATS document, *The Diagnosis and Initial Management of Non-Malignant Disease Related to Asbestos,* which says "the carbon monoxide diffusion capacity is commonly reduced ... although a low diffusion capacity is often reported *as the most sensitive indicator of early asbestosis*, it is also a relatively nonspecific finding" (p 7 in ATS document).

(10) Dr. Weill expressed the opinion that asbestosis must be present in an individual in order to attribute that person's lung cancer to asbestos exposure, and in stating this opinion he relies primarily on two studies, one by Hughes and the other by Sluis-Cremer.

The study by Hughes including only 839 exposed men and there were only 29 deaths from lung cancer; the small sample size severely limits the power of the study to detect true risks. This study compared the likelihood of lung cancer among asbestos cement plant workers with asbestosis to those workers with at least 21.5 years of work but without asbestosis. The group with asbestosis had a higher risk for lung cancer, but this group also was older, had a higher cumulative exposure to asbestos and was also more likely to have smoked cigarettes than the group without asbestosis. As I described in my prior report, numerous studies and expert reviews show that there is a dose-response relationship between exposure to asbestos and the risk of lung cancer, with increasing exposure leading to increasing risk of disease. Workers with asbestosis do have a two to four fold higher risk of lung cancer than asbestos exposed workers without asbestosis, but in this case the asbestosis may simply be a surrogate measure of exposure; significant asbestos exposure is required to cause asbestosis.

The other study looked at the relationship between asbestosis found on pathologic examination of the lung among 339 asbestos miners and lung cancer. Pathology is not medically necessary for clinical diagnosis and is almost never used for that purpose; there is no consideration of requiring pathological examination of a lung before determining whether a lung cancer is caused by asbestos, since the individual would have to have an extensive surgical procedure, or be dead, to have a pathological examination performed. As described in my prior report, asbestosis can be present pathologically when the chest x-ray is normal, and there is widespread agreement that a high resolution CT scan can detect asbestosis when the chest x-ray is normal. Both of these findings tell us that requiring asbestosis to be present on a chest x-ray would exclude a number of individuals with asbestosis on high resolution CT scan or on pathologic examination of the lung. Because the chest x-ray is not a good measure of pathologic asbestosis, and because we would not require pathologic examination of the lung in all claimants with lung cancer, the study by Sluis-Cremer is not relevant to the questions before the court in this case.

To understand the relationships between asbestos exposure, asbestosis and lung cancer, several important characteristics of radiologically detectable asbestosis must be described. One, the likelihood of developing asbestosis increases with the amount of asbestos dust inhaled. Second, workers who smoke have a higher likelihood of developing asbestosis, because of reduced

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plaques in asbestos-exposed workers: reproducibility of a new high-resolution CT visual semiquantitative measurement method. J Thorac Imaging. 2006 Mar;21(1):8-13

clearance of asbestos from the lung (smoking damages the lungs' defense mechanisms). Third, asbestosis is a disease that generally takes 15 or more years to develop. All three factors also describe the likelihood of developing an asbestos-related cancer: the risk of lung cancer increases with increasing dose, there is a higher risk of lung cancer in a smoker than in a non-smoker, and there is generally at least a 15 year delay between the onset of exposure and the development of a lung cancer. Therefore it is clear that workers with asbestosis will have a higher risk of lung cancer than workers without asbestosis, on average, since they have had more exposure to asbestos and are more likely to have been smokers, not necessarily because asbestosis is a necessary intermediate step.

There is a risk of lung cancer in other types of diffuse pulmonary fibrosis, but only of one cancer cell type, adenocarcinoma. If lung cancer arises from the scars caused by asbestosis, the excess cancers should all be adenocarcinomas. Instead, the rates of all types of lung cancer are elevated in asbestos-exposed workers, and the distribution of the different lung cancer cell types is indistinguishable from the patterns seen in cigarette smokers not exposed to asbestos. The rates of lung cancer seen among other types of pulmonary fibrosis are also much lower than the rate seen after exposure to asbestos. Both the much higher risk of lung cancer after asbestos exposure, and the increase in cell types other than adenocarcinoma, demonstrate that lung cancer in asbestos exposed groups is not simply a "scar cancer".

The question at issue is whether workers without asbestosis have a risk of lung cancer increased above that of the general population, not whether workers with asbestosis have a higher risk of lung cancer than workers without asbestosis. Many well-conducted epidemiological studies support a direct relationship between asbestos exposure and risk of lung cancer, and show an elevated risk of lung cancer in asbestos-exposed workers in general. An international group developed the Helsinki Criteria for attribution of lung cancer in asbestos exposed workers, and concluded that an exposure of 25 fiber-years, in the absence of any other disease, doubles the risk for lung cancer; this expert consensus has been supported by additional research and analysis. [16]

(11) Dr. Weill expressed the opinion that asbestosis does not contribute to obstructive lung disease, and refers to a study of 2611 long-term asbestos insulators (Miller 1994) to support his opinion. That study reaches the opposite conclusion, finding that asbestos exposure predicted a

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[16] Reid A, de Klerk N, Ambrosini GL, Olsen N, Pang SC, Berry G, Musk AW. The effect of asbestosis on lung cancer risk beyond the dose related effect of asbestos alone. Occup Environ Med. 2005 Dec;62(12):885-9; Finkelstein MM. Radiographic asbestosis is not a prerequisite for asbestos-associated lung cancerin Ontario asbestos-cement workers. Am J Ind Med. 1997 Oct;32(4):341-8; Wilkinson P, Hansell DM, Janssens J, Rubens M, Rudd RM, Taylor AN, McDonald C. Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph? Lancet. 1995 Apr 29;345(8957):1074-8; Cullen MR, Barnett MJ, Balmes JR, Cartmel B, Redlich CA, Brodkin CA, Barnhart S, Rosenstock L, Goodman GE, Hammar SP, Thornquist MD, Omenn GS. Predictors of lung cancer among asbestos-exposed men in the {beta}-carotene andretinol efficacy trial.Am J Epidemiol. 2005 Feb 1;161(3):260-70; Henderson DW, Rodelsperger K, Woitowitz HJ, Leigh J. After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997-2004. Pathology. 2004 Dec;36(6):517-50.

decrease in FEV1/FVC. The FEV1/FVC ratio is the best measure of obstructive lung disease on spirometry. In the study by Miller at el, a regression analysis was used to take into account smoking, the presence of asbestosis, duration since onset of exposure; both asbestosis and duration since onset of exposure predicted obstructive lung disease as measured by the FEV1/FVC. Miller did find that the predominate effect of asbestos exposure is to cause a reduction in lung volume (restrictive lung disease), and that smoking was the more important predictor of obstructive lung disease, but there was an important effect of asbestos exposure on obstruction as well.

Most asbestos exposed workers are current or former smokers; in the Miller 1994 study only 19.7% were non-smokers, and among sheet metal workers only 20-25% were lifelong non-smokers. [17]. The practical effect of the high rate of smoking among asbestos exposed workers is that most will have a combination of obstructive disease (from smoking with an added small contribution from asbestos exposure) and restrictive disease (from asbestos exposure). Therefore any medical criteria for the diagnosis of asbestosis which include the FEV1/FVC ratio must take into account this attribute of the population at risk, and recognize that many workers with asbestosis will have a mixture of obstructive and restrictive lung disease.

(12) Dr. Weill proposes that, as part of the measurement of impairment, a claimant for asbestos-related lung disease must have an FEV1/FVC ratio greater than 65% as an absolute value. The National Heart, Lung, and Blood Institute/World Health Organization GOLD criteria on the standards for the diagnosis and treatment of COPD use a fixed ratio of 70% for the diagnosis of obstructive lung disease, and. the LLN of the FEV_1/FVC ratio is < 70% for many older individuals.[18] For example, in a 2002 study of elderly, nonsmoking, healthy participants the authors demonstrated that of subjects who were > 70 years old, 35% had an FEV_1/FVC ratio of < 70%, as did approximately 50% of subjects who were > 80 years of age. [19] Setting a level of the FEV1/FVC ratio at 65% for all claimants will essentially preclude any component of obstructive lung disease in a substantial fraction of workers with asbestosis, given that workers with asbestosis are often now over 70 years old.

(13) Dr. Weill expressed the opinion that impairment should be defined as the presence of a total lung capacity less than 80% of predicted, a forced vital capacity less than 80% of predicted, and an FEV1/FVC ratio of greater than 65%. He cites the Guide to the Evaluation of Impairment, from the American Medical Association, as a source for his opinion. The AMA Guides do not require a total lung capacity to make a determination of impairment. The only reference in the Guides to the FEV1/FVC ratio is in the definition of a normal spirometry. The FEV1/FVC ratio is used in determination of whether or not the lung disease is due to obstruction or restriction, and a reduction in the ration in itself is not a measure of impairment. The FEV1/FVC ratio is part of the

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[17] Welch LS, Michaels D, and Zoloth S. Asbestos-Related Disease among Sheet Metal Workers. American Journal of Industrial Medicine 25:635-48, 1994

[18] Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global Strategy for the Diagnosis, Management, and Prevention of COPD - 2006 Update. Am J Respir Crit Care Med. 2007 May 16; [Epub ahead of print]

[19] Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Mørkve O. Eur Respir J. 2002 Nov;20(5):1117-22

assessment of the *cause* of impairment and so should not be included in impairment assessment per se.

(14) Dr. Weill presents the results of an analysis of pulmonary function testing (PFTs) submitted as part of claims for asbestos-related disease. He reviewed a 10% sample of submitted claims, reviewing 150 files. He concludes that all but 10/150 tests fail to comply with American Thoracic Society testing criteria for spirometry, and that none had tests that complied with all testing criteria for spirometry, FRC, and DLCO.

These were pulmonary function tests taken in screening programs, and in many cases were likely to have been performed on mobile testing equipment. It would be unlikely therefore that all the tests *recommended* (not required) by the American Thoracic Society for the evaluation of asbestos-related disease would be included in such an examination. The ATS recommends that the evaluation of asbestos-related disease include spirometry, all lung volumes and diffusion capacity, although the ATS statement does not set a minimum set of tests required for the diagnosis. None of the 150 tests reviewed by Dr. Weill included a total lung capacity. Total lung capacity generally cannot be provided in a mobile environment, nor is total lung capacity required for the diagnosis of asbestosis under most algorithms. Therefore Dr. Weill is applying an unnecessarily high bar to these screening medical examinations by requiring that they include total lung capacity when that is generally not required for diagnosis.

Dr. Weill also set a high bar for determining whether the spirometry he reviewed conformed to the ATS criteria for acceptable spirometry. The ATS recommends that pulmonary function should be determined from a series of at least three acceptable forced expiratory curves. When Dr. Weill reviewed these 150 tests he looked first to see whether three tracings (the visual presentation of the effort made during the test) were attached to the report. If the actual tracings were not attached he then looked to see whether there were three sets of numerical results. If there were not three numerical results included in the report the spirometry was considered unacceptable.

There are many different spirometers used in the United States, and there are a range of ways these spirometers present test results. A typical printout would report the best effort, the number of efforts, and the difference between the best efforts and the next best effort (either in milliliters or as a percentage). This printout would include all of the information required by the ATS, for it would report that three acceptable efforts were done and that the difference between the best and next best effort met the reproducibility criteria. However, this printout would not include the numerical results of all three efforts. The computers built into spirometers perform the calculations, and rarely are the tracings and graphs found n a medical file, nor is it necessary to review the graphs to assess whether or not spirometry complies with the ATS standards. Yet Dr. Weill did not allow a spirometric test to be acceptable if the information was presented in this alternate format.

The results reviewed by Dr. Weill were collected during screening examinations, not diagnostic examinations, and there are important differences between screening and diagnosis. Medical screening is the search for previously unrecognized disease, when finding the disease can lead to a benefit. Mammography is a well-accepted screening test, for example, since it has been shown to improve life expectancy for breast cancer in those for whom a cancer is found early with

screening; the same is true for colon cancer screening, skin cancer screening, and others. Screening tests, in general, are chosen to be easily administered, at low or reasonable cost, and to be sensitive – the goal is to find as many cases of disease as possible, and at an early stage, even if "false-positives" are detected. Occupational screening programs are designed to detect work-related disease at an early stage, when treatment or removal from exposure can improve the outcome of that disease. Additional tests often are needed to make a final diagnosis.

(15) Dr. Henry coordinated a claimant x-ray study in which he had three B readers classify 807 claimant x-rays submitted by a group of plaintiff law firms under a court order. Dr. Henry classified an agreement between the independent readings and the claimant readings only if two of the three independent B readers agreed with the claimant reading. In my opinion agreement should have been considered to be present if one of the independent readers agreed with the claimant; in that case you would have two readers calling the film abnormal and two calling it normal. Requiring that two of three readers classify a film as abnormal before the film is accepted as abnormal will exclude many cases with asbestosis.

I was able to review the data underlying Dr. Henry's report. The claimant B reader classified 461 films in the sample, of which 371 were read as 1/0 or higher using the ILO classification; the remaining 90 were classified by the claimant reader as negative for parenchymal disease. At least one of Dr. Henry's consultant readers classified 66 of these as $\geq$ 1/0, for an agreement of 17.8% between one or more consultant reader and the claimant reader. For the 90 films classified as negative ($<$ 1/0) by the claimant reader, all three of Dr. Henry's readers agreed the film was negative; if we combine all films read by all 4 readers there was agreement with the claimant reader 33.4% of the time by one or more comparison readers.

Dr. Henry's three consultant readers did not always agree with each other. For example, one consultant reader agreed with the claimant reader on 14.4% of the claimant reader's positive films; that same reader agreed 40% and 50% with the positive films of Dr. Henry's other two readers. Although a 40% agreement clearly is higher than a 14% agreement, this difference is not as extreme as presented by Dr. Henry. Dr. Henry stated that the claimant reader reported the presence of small opacities 11 times more frequently than the comparison readers; my analysis shows that difference to be less than 3 fold. A three fold difference in classification is well within the range of inter-reader variability reported by Ducatman, who found that in an analysis of more than 105,000 radiographs, which had been read by 23 different B readers, there was a 300-fold variation in the prevalence of findings of parenchymal abnormalities. [20] Among these 23 B readers were 6 instructors for the NIOSH B reading course; there was more than a 10 fold difference among these recognized experts.

Dr. Henry states in his conclusion that both the ILO and NIOSH guidelines recommend the use of three independent readers to generate more reliable results. In the 2000 revision of the ILO guidelines there is a recommendation that 3 B readers be included for an epidemiologic study. There is no recommendation for multiple B readings when the ILO classification is used for clinical purposes. The NIOSH web page for respiratory diseases states in the section regarding

[20] Ducatman, Am, Yang WN, Foreman SA. B-Readers and Asbestos Medical Surveillance. JOEM 1988 30:644-7

Worker Monitoring and Surveillance that "*Number of readers and summary classifications*: A single B Reader classification of each chest radiograph is generally sufficient..." [21] In addition, the Occupational Safety and Health Administration (OSHA) asbestos standard requires that chest radiographs obtained for surveillance of those exposed to asbestos be interpreted and classified by a B Reader, radiologist, or physician with expertise in pneumoconiosis; there is no requirement for multiple readings. The ILO and NIOSH do recommend the use of multiple B readers for epidemiologic studies of workers exposed to asbestos; the issue at hand here is clinical diagnosis of individual patients, not epidemiological studies.

The ILO classification system was not designed to be used as a diagnostic test, and the diagnosis of asbestosis requires more than an X-ray interpretation, as discussed by the American Thoracic Society in the guidelines for the clinical diagnosis of non-malignant lung disease related to asbestos. [22] A single X-ray classification is subject to observer variability, as has been shown in Ducatman's study and others, and should not be used as the only criterion for a diagnosis of asbestos-related disease. There are additional and medically necessary steps to reach an asbestosis diagnosis.

Like so many other aspects in the practice of medicine, the reading of an x-ray is a medical judgment. Each clinician has to use judgment and skill when using the ILO classification just as when he/she looks at other test results. In medicine, the majority is not always right. We all have heard of cases where 2, 3, even 4 doctors will miss the diagnosis, and then a 5th doctor looks at the same patient, reaches the right diagnosis, and saves the patient's life. Would we conclude that the majority was right and that last doctor wrong? The only way to know for sure that asbestosis is present would be to examine the lung with pathology, but that is clearly not an option in most cases. Short of examining the lung in every possible case of asbestosis, we need to accept some variation between B readers, and therefore some degree of uncertainty; the certainty of the diagnosis of asbestosis is enhanced by following the guidelines in the 2004 American Thoracic Society document, *The Diagnosis and Initial Management of Non-Malignant Disease Related to Asbestos*.

(16) Dr. Moolgavkar includes criticisms of the ATSDR medical testing study in his report. He cites as a limitation that the x-ray readers were not blinded to the source of the radiographs and that no controlled radiographs were included. This study was not designed to be an epidemiologic study; it was an assessment of the health effects in the Libby Montana area. The National Institute for Occupational Safety And Health provides recommendations for ILO classification in different settings. Under worker monitoring and surveillance the guidelines specifically say that blinded classification is *undesirable,* in order to facilitate disease detection where individuals are potentially at risk. [23]

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[21] http://www.cdc.gov/niosh/topics/chestradiography/radiographic-classification.html

[22] American Thoracic Society. Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos. Am J Respir Crit Care Med 170:691-715 2004

[23] http://www.cdc.gov/niosh/topics/chestradiography/radiographic-classification.html

(17) Dr. Moolgavkar criticizes Dr. Whitehouse for using the normative predictive values published by Knudson in 1983, saying that these normative values would be out of date. Dr. Moolgavkar must be unaware of that many of the spirometers used in the United States have the Knudson predictive values as one of the options for predicting the normal value of pulmonary function, and that these predictive values have been considered the gold standard in many epidemiologic studies.

(18) Dr. Moolgavkar criticizes Dr. Whitehouse for not presenting evidence on cross calibration of the two different models Dr. Whitehouse used to do pulmonary function testing. Equipment used to test pulmonary function is designed to meet ATS standards, and by meeting ATS standards the machines are therefore comparable with each other. Lung function testing can be done on a hundred different machines; if the machines meet the ATS standards and the PFT measurements on those machines also meet the ATS standards, the results are comparable.

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